upon treatment of **19e** with cyanotrimethylsilane–titanium tetrachloride (eluting with 1:1 hexanes–ether), as a yellow oil: ^{1}H NMR δ 7.02 (d, 1, J = 8 Hz, C-6 H), 6.42 (m, 2, C-3, C-5 H), 5.30 (s, 1, OH), 3.80 (s, 3, OCH_3), 3.54 (s, 3, OCH_3), 2.76 (m, 2, CH_2), 2.08 (m, 2, CH_2), 1.60 ppm (s, 3, CH_3); MS m/z 235 (M^+).

***rac*-2-Hydroxy-α-methoxy-4-(phenylmethoxy)benzenebutanenitrile (38).** This compound was isolated, in 19% yield, by chromatography, on silica gel, of the reaction mixture obtained upon treatment of **19a** with cyanotrimethylsilane–titanium tetrachloride (eluting with 1:1 hexanes–ether) as an oil which crystallized on standing: ^{1}H NMR δ 7.40 (m, 5, $C_6H_5CH_2$), 7.00 (d, 1, J = 8 Hz, C-6 H), 6.47 (m, 2, C-3, C-5 H), 5.13 (s, 1, OH), 5.02 (s, 2, $C_6H_5CH_2O$), 4.01 (dd, 1, J = 2,6 Hz, CHCN), 3.54 (s, 3, OCH_3), 2.76 (t, 2, J = 7 Hz, CH_2), 2.16 ppm (m, 2, CH_2); MS m/z 297 (M^+).

Typical Procedure for Hydrolysis of the 3,4-Dihydro-2*H*-1-benzopyran-2-carbonitriles: *rac*-3,4-Dihydro-7-(phenylmethoxy)-2*H*-1-benzopyran-2-carboxylic Acid. A mixture of 0.265 g (1 mmol) of nitrile **36a**, 0.5 g (7.68 mmol) of pulverized 86% potassium hydroxide, 4 mL of ethylene glycol, and 0.3 mL of water was stirred and heated (150 °C oil bath) for 4.5 h. The resulting solution was cooled, diluted with water, and extracted twice with ether (the ether extracts were discarded). The aqueous alkaline solution was acidified with 3 N HCl, leading to the formation of a white precipitate, which was isolated by workup with ether in the usual manner. There was obtained 0.283 g (99.6%) of the acid as a colorless solid: mp 127–129 °C; ^{1}H NMR δ 5.03 (s, 2, OCH_2Ph), 4.70 (dd, 1, J = 4,8 Hz, CHO); MS m/z 284 (M^+). The analytical specimen was obtained from a separate experiment as a colorless solid, mp 129–130.5 °C (from ethyl acetate–hexanes).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.00; H, 5.65.

Acknowledgment. We are grateful to the staff of the Physical Chemistry Department, Hoffmann-La Roche, Inc., Nutley, NJ, for obtaining many of the spectral and microanalytical measurements required in this work.

Supplementary Material Available: Tables of crystal data, final atomic parameters, final anisotroic thermal parameters, bond lengths and angles, and perspective drawings of **26** and **29f** and elemental analyses (13 pages). Ordering information is given on any current masthead page.

Palladium(0)-Catalyzed Azidation of Allyl Esters. Selective Synthesis of Allyl Azides, Primary Allylamines, and Related Compounds

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Palladium(0)-catalyzed reaction of allyl esters such as phosphates, carbonates, and carboxylates with sodium azide gives allyl azides. The azidation proceeds with retention of configuration at the allylic carbon. Optically active (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl azide (**19**) is obtained from (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl acetate (**18**) stereoselectively. Sequential substitution of (*Z*)-4-acetoxy-2-buten-1-yl diethyl phosphate (**24**) with nucleophiles and subsequently azide ion gives (*E*)-4-substituted-2-buten-1-yl azides **27**. The reaction of allyl azides with triphenylphosphine gives iminotriphenylphosphoranes, which are versatile synthetic intermediates of primary allylamines, *N*-allylimines, and *N*-allylamides. Treatment of allyl azides with triphenylphosphine and subsequently with aqueous ammonium solution gives primary allylamines. Other synthetic applications of allyl azides are also described.

The growing importance of primary allylamines as enzyme inhibitors[1] and biologically active substances has led to the development of new synthetic methods for primary allylamines.[2,3]

Palladium-catalyzed amination of allylic compounds with secondary amines has been extensively studied and proved to be efficient for the synthesis of tertiary amines,[4] and various nitrogen-containing biologically active compounds such as alkaloids have been synthesized.[5] However, the palladium-catalyzed reactions with ammonia or primary amines cannot be applied to the synthesis of primary or secondary allylamines, because polyallylation results in contamination of secondary and tertiary allylamines. Therefore, for the synthesis of primary allylamines, preparation of N-protected primary allylamines, such as 4,4′-dimethoxybenzhydrylamine,[6] *p*-toluenesulfonamide,[7] phthalimide,[8] and di-*tert*-butyl iminodi-

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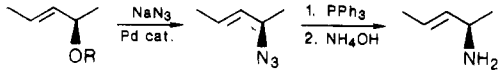
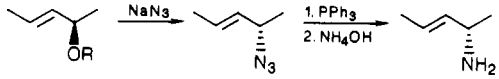
carbonate,[9] by palladium-catalyzed reactions and subsequent removal of the protecting groups has been utilized. For the synthesis of secondary allylamines, preparations of *N*-allylhydroxylamines by palladium-catalyzed reactions and subsequent reduction have been utilized.[10]

Recently, we found that the palladium(0)-catalyzed reaction of allyl esters with azide ion gives the corresponding allyl azides under mild conditions with net retention of configuration (eq 1).[11] The stereochemical course is opposite to that of S_N2 type azidation (eq 2).[12] Allyl azides



(1)



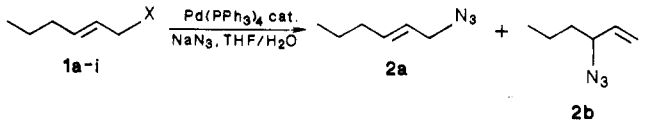
(2)

thus obtained are versatile synthetic intermediates such as 1,3-dipoles[13] and precursors of various substances such as nitrenes.[14] Primary allylamines can be prepared from the corresponding allyl esters stereoselectively by one-pot reactions. Treatment of allyl azides thus obtained with triphenylphosphine and subsequently with aqueous ammonium solution gives primary allylamines highly efficiently.

This paper describes the full scope of the palladium-catalyzed azidation of allyl esters, stereochemistry, mechanism, and synthetic applications, particularly synthesis of primary allylamines.

Results and Discussion

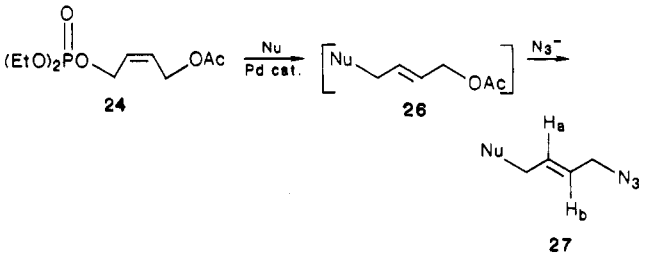
Palladium-catalyzed reactions of allyl esters such as allyl acetates and allyl phosphates with azide anion give allyl azides highly efficiently. The azidation of (*E*)-2-hexen-1-yl derivatives **1a–i** was examined in detail as a typical example. (*E*)-2-Hexen-1-yl phosphate **1a** and acetate **1e** did not react with sodium azide in aqueous THF; however, the addition of 2 mol % of $Pd(PPh_3)_4$ induced the azidation dramatically to give a mixture of 2-hexen-1-yl azide (**2a**) and 1-hexen-3-yl azide (**2b**) (eq 3). The ratio of allyl azides



(3)

2a and **2b** (70:30) is at equilibrium because of rapid 1,3-rearrangement.[15] The reactivity of the leaving groups of various esters has been found to be in the order $(EtO)_2PO_2^-$ (**1a**) ~ $EtOCO_2^-$ (**1b**) ~ $CF_3CO_2^-$ (**1c**) ~ $PhCO_2^-$ (**1d**) ≥ $CH_3CO_2^-$ (**1e**). The catalytic activity of various palladium complexes for the azidation of (*Z*)-5-(methoxycarbonyl)-2-cyclohexen-1-yl acetate (**3**) at 50 °C is in the order $Pd(PPh_3)_4$ ~ $Pd_2(dba)_3{\cdot}CHCl_3$–$4PPh_3$ > $Pd(acac)_2$–$2PPh_3$. $Pd_2(dba)_3{\cdot}CHCl_3$–$4PPh_3$ is more reactive than $Pd(dba)_2$–$2PPh_3$. The reaction requires about 20% of water in order to dissolve sodium azide. The solvent effect for the conversion of **3** and the yield of the product are in the order THF > DME > DMF ~ acetone > CH_3CN ~ EtOH ~ hexane ~ toluene.

Scheme I

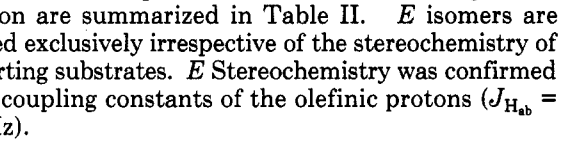


The representative results of the $Pd(PPh_3)_4$-catalyzed azidation of various allyl esters in aqueous THF are summarized in Table I. The azidations of geranyl (**5**), linalyl (**6**), and neryl acetates (**7**) at 40 °C for 30 min gave the same mixture of geranyl azide (**8a**) and linalyl azide (**8b**) (80:20) respectively, although the conversions of **5** and **7** were 25% and that of **6** was 94%. The azidations of **5** and **7** at 50 °C for 2 h gave **8a** and **8b** in 64% and 79% isolated yields, respectively. (*E*)- and (*Z*)-Cinnamyl diethyl phosphates (**16, 17**) were converted into (*E*)-cinnamyl azide (**15**) irrespective of the stereochemistry of the starting substrate. The reaction of allyl acetates bearing an electron-withdrawing group such as Ph, CN, or COOR gave the thermodynamically more stable conjugated allyl azides exclusively. The palladium(0)-catalyzed azidation of allyl phosphates under anhydrous conditions is performed by using trimethylsilyl azide ($TMSN_3$) in the presence of Bu_4NF, although the same treatment with allyl acetates was unsuccessful.

Generally, the reactivity of allyl phosphates is much higher than that of allyl acetates. Typically, the azidation of (*Z*)-4-acetoxy-2-buten-1-yl diethyl phosphate (**24**)[4f] with 1 equiv of azide ion gave a mixture of (*E*)-4-azido-2-buten-1-yl acetate (**25a**) and 2-azido-3-buten-1-yl acetate (**25b**) (80:20) in 92% yield. Palladium-catalyzed sequential substitution of **24** gives (*E*)-4-substituted-2-buten-1-yl azides **27** selectively (Scheme I). Amination and alkylation of **24** at room temperature give 4-substituted 2-buten-1-yl acetate (**26**), which undergoes the azidation without isolation of **26**. The representative results of the sequential azidation are summarized in Table II. *E* isomers are obtained exclusively irrespective of the stereochemistry of the starting substrates. *E* Stereochemistry was confirmed by the coupling constants of the olefinic protons ($J_{H_{ab}}$ = ~15 Hz).

Quite recently, Waegell reported that palladium-catalyzed reaction of 1,3-diene monoepoxides with azide ion gives 4-azido-2-alkenols regioselectively.[16]

The stereochemical course of the azidation was examined precisely in the case of the azidation of (*Z*)-5-(methoxycarbonyl)-2-cyclohexen-1-yl esters (eq 4). The reaction



(4)

3: OR = OAc
34: OR = OP(O)(OEt)$_2$
4a **4b**

of acetate **3** with sodium azide in the presence of 5 mol % of $Pd(PPh_3)_4$ at 50 °C for 2 h gave a mixture of (*Z*)- and

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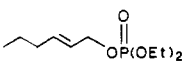
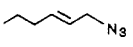
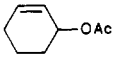
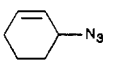
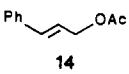
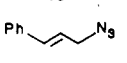
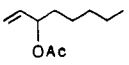
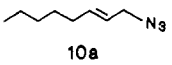
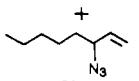
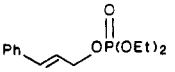
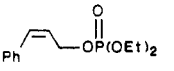
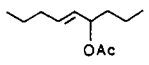
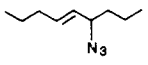
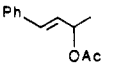
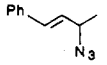
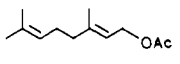
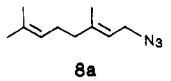
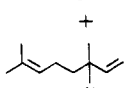
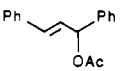
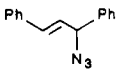
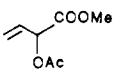
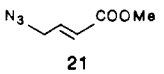
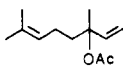
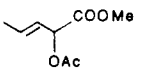
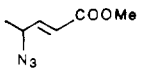
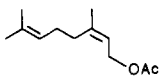
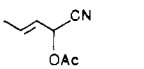
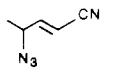
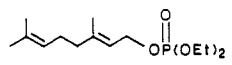
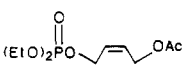
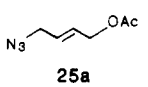
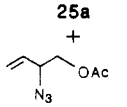
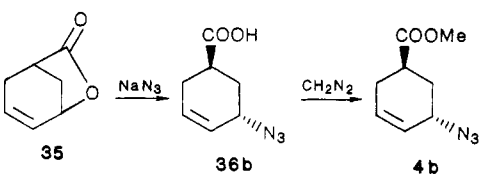
Table I. Palladium-Catalyzed Azidation of Allyl Esters[a]

allyl ester	allyl azide	yield,[b] % (ratio of α:γ[c])	allyl ester	allyl azide	yield,[b] % (ratio of α:γ[c])
 **1a**	 **2a** +  **2b**	78[d] (70:30)		 **13**	70
			 **14**	 **15**	92
 **9**	 **10a** +  **10b**	97 (70:30)	 **16**	**15**	82, 85[e]
			 **17**	**15**	73
 **11**		94	 **18**	 **19**	95
 **5**	 **8a** +  **8b**	64 (80:20)		 **20**	96
				 **21**	96
 **6**	**8a + 8b**	91 (80:20)		 **22**	60
 **7**	**8a + 8b**	79 (80:20)		 **23**	80
 **12**	**8a + 8b**	83, 85[e] (80:20)	 **24**	 **25a** +  **25b**	92 (80:20)

[a] The reaction was carried out according to the general procedure described in the Experimental Section. [b] Isolated yield by column chromatography (SiO_2). [c] The ratio of α and γ allyl azides was determined by ^1H NMR analysis. [d] The solvent is diethyl ether. [e] $TMSN_3/Bu_4NF$ was used in dry THF.

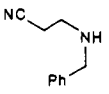
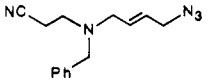
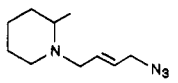
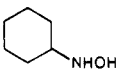
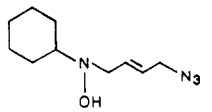
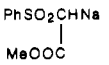
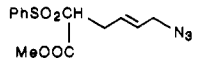
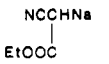
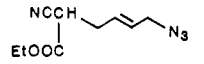
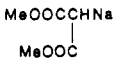
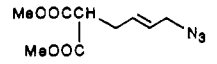
(*E*)-methyl 5-azido-3-cyclohexenecarboxylate (**4a** and **4b**) (38:62) in 92% yield. The addition of 2 equiv of 1,4-bis(diphenylphosphino)butane (dppb) resulted in a drastic change of the ratio **4a**:**4b** (84:16), although the yield became low (38%). Therefore, the effect of various palladium catalysts was examined precisely. The typical results are summarized in Table III. The addition of a bidentate phosphine such as 1,4-bis(diphenylphosphino)butane (dppb), 1,3-bis(diphenylphosphino)propane (dppp), 1,5-bis(diphenylphosphino)pentane, or 1,1′-bis(diphenylphosphino)ferrocene (dppf) to $Pd_2(dba)_3{\cdot}CHCl_3$ resulted in highly stereoselective azidation. The reactivity of $Ph_2P(CH_2)_nPPh_2$ is in the order $n = 1 << 2 < 3 < 4 < 5 <$ ferrocenyl; however, considering the selectivity of **4a**/**4b**, dppb seems to be the best ligand. The addition of 4 equiv of dppb gave the best result for the formation of **4a**, although the addition of a large excess of dppb decreased the yield of **4**.

Phosphorylation of (*Z*)-methyl 5-hydroxy-3-cyclohexenecarboxylate with diethyl chlorophosphate afforded (*Z*)-diethyl 5-(methoxycarbonyl)-2-cyclohexen-1-yl phosphate (**34**) stereoselectively. Stereochemical assignment of **34** was based on the ^1H NMR (100 MHz) spectrum. The proton resonance at δ 2.85 (1 H, ddd, J = 12.3, 12.3, and 9.4 Hz) was assigned as the C-6 axial hydrogen. The large geminal coupling as well as two large vicinal coupling constants clearly indicates that the protons at C-1 and C-5 are pseudoaxial, thus confirming the *Z* configuration. The ^{31}P NMR spectrum of (*Z*)-**34** appears at δ −1.25 as a single product, and no absorption of the (*E*)-phosphate at δ −1.53 was detected. The reaction of phosphate **34** with NaN_3 in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$–dppb catalyst gave **4a** highly stereoselectively in 99% yield (**4a**:**4b** = 97:3). In contrast, direct S_N2 substitution of 7-oxabicyclo[3.2.1]-oct-2-en-6-one (**35**) with NaN_3 at 50 °C gave **36b** in 83% yield along with 2% of **36a**. Furthermore, the azidation



35 **36b** **4b**

Table II. Sequential Azidation of (*Z*)-4-Acetoxy-2-buten-1-yl Diethyl Phosphate (24)

entry	Nu_1	Nu_2	product	yield,[a] %
1		NaN_3	 **28**	76
2		NaN_3	 **29**	80
3		NaN_3	 **30**	92
4		NaN_3	 **31**	78
5		NaN_3	 **32**	75
6		NaN_3	 **33**	76

[a] Isolated yields by column chromatography.

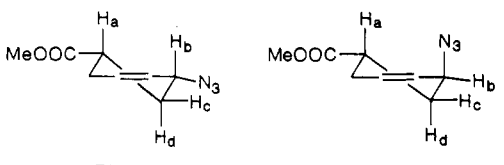
Table III. Palladium Catalysts for the Azidation of 3[a]

entry	Pd cat.	ligand	conv,[b] %	yield of 4,[b] %	ratio[b] 4a:4b
1	$Pd(PPh_3)_4$	none	100	92	38:62
2	$Pd(PPh_3)_4$	LiCl[c]	100	98	38:62
3	$Pd(PPh_3)_4$	2 dppb	41	38	84:16
4	$Pd_2(dba)_3{\cdot}CHCl_3$	4 PPh_3	74	72	71:29
5	$Pd_2(dba)_3{\cdot}CHCl_3$	2 $Ph_2PCH_2PPh_2$	2	2	92:8
6	$Pd_2(dba)_3{\cdot}CHCl_3$	2 $Ph_2P(CH_2)_2PPh_2$	13	5	92:8
7	$Pd_2(dba)_3{\cdot}CHCl_3$	2 $Ph_2P(CH_2)_3PPh_2$	57	41	95:5
8	$Pd_2(dba)_3{\cdot}CHCl_3$	1 dppb	22	22	88:12
9	$Pd_2(dba)_3{\cdot}CHCl_3$	2 dppb	71	56	91:9
10	$Pd_2(dba)_3{\cdot}CHCl_3$	4 dppb	95	92	91:9
11	$Pd_2(dba)_3{\cdot}CHCl_3$	4 dppb	80	77	96:4[d]
12	$Pd_2(dba)_3{\cdot}CHCl_3$	8 dppb	99	45	91:9
13	$Pd_2(dba)_3{\cdot}CHCl_3$	2 $Ph_2P(CH_2)_5PPh_2$	100	80	76:24
14	$Pd_2(dba)_3{\cdot}CHCl_3$	2 dppf[e]	100	86	82:18
15	$Pd_2(dba)_3{\cdot}CHCl_3$	2 TRIPHOS[f]	38	28	94:6
16	$Pd(acac)_2$	2 PPh_3	78	65	49:51
17	$Pd(acac)_2$	2 dppb	14	9	79:21
18	$Pd(PCy_3)_2$	none	14	2	55:45
19	$Pd(PCy_3)_2$	2 dppb	11	10	68:32
20	$Pd(dba)_2$	2 PPh_3	25	17	91:9
21	$Pd(dba)_2$	2 dppb	2	2	91:9
22	$Pd(OAc)_2$	2 dppb	1	1	90:10
23	$Pd(CF_3CO_2)_2$	2 PPh_3	1	1	62:38

[a] A mixture of 3 (0.50 mmol), palladium catalysts (5 mol %), ligand, and NaN_3 (0.55 mmol) in THF (2.0 mL) and water (0.5 mL) was stirred at 50 °C for 2 h under Ar. [b] GLC analysis. [c] An equimolar amount was used. [d] Palladium catalyst (2 mol %). [e] 1,1′-Bis(diphenylphosphino)ferrocene. [f] Bis[2-(diphenylphosphino)ethyl]phenylphosphine.

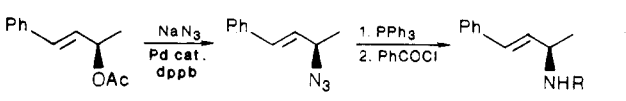
of lactone **35** in the presence of $Pd(OAc)_2$–$2PPh_3$ catalyst gave (*Z*)-azido carboxylic acid **36a** in 92% yield (*E*:*Z* = 5:95). The acid **36b** was converted into **4b** upon treatment with diazomethane.

The stereochemistry of **4a** and **4b** thus obtained was established by their NMR spectra. In the case of **4a**, the proton resonance at δ 1.72 (1 H, ddd, *J* = 12.6, 12.6, and 10.3 Hz) is assigned as the C-6 axial hydrogen (H_d). A large geminal coupling constant as well as two large vicinal coupling constants ($J_{H_{ad}}$ = 12.6 Hz, $J_{H_{bd}}$ = 10.3 Hz, and $J_{H_{cd}}$ = 12.6 Hz) clearly indicates that the protons at C-1 (H_a) and C-5 (H_b) are pseudoaxial, indicating the *Z* configuration. In the case of **4b**, the resonances at δ 1.90 (ddd, *J* = 13.8, 11.9, 4.8 Hz, H_d) and at δ 2.13 (ddd, *J* = 13.8, 3.09, 3.09 Hz, H_c) are readily discernible with the expected coupling constants of $J_{H_{ac}}$ = 4.8 Hz, $J_{H_{ad}}$ = 11.9 Hz, $J_{H_{bc}}$



(*Z*)-**4a** (*E*)-**4b**

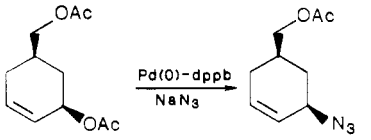
Scheme II



(*R*)-**18** (*R*)-**19** (*R*)-**39**: R = H; (*R*)-**40**: R = COPh

= 3.09 Hz, J_{H_bd} = 3.09 Hz, and J_{H_cd} = 13.8 Hz, suggesting that H_a and H_b are pseudoaxial and equatorial, respectively.

The $Pd(PPh_3)_4$-catalyzed azidation of **3** gave a mixture of **4a** and **4b** (38:62) with a low selectivity. In order to avoid the epimerizations of **3** and **4** at the α-position of methyl carboxylate under the reaction conditions, we examined the azidation of **37** (eq 5). The $Pd_2(dba)_3$·$CHCl_3$–dppb-catalyzed azidation of **37** (*Z*:*E* = 96:4) gave (*Z*)-5-(acetoxymethyl)-2-cyclohexen-1-yl azide (**38**) (*Z*:*E* = 93:7). However, the $Pd(PPh_3)_4$-catalyzed azidation of **37**



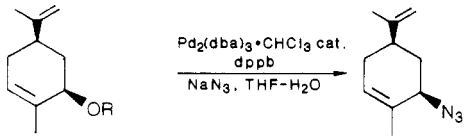
(5)

Z:*E* = 96:4 **37** *Z*:*E* = 93:7 **38**

under the same conditions gave a mixture of (*Z*)- and (*E*)-**38** (54:46). The stereoselectivity seems to be strongly affected by the intermediate (π-allyl)palladium species.

Next, we examined catalytic transformation of (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl acetate (**18**) by using $Pd_2(dba)_3$·$CHCl_3$–dppb as catalyst. The azidation of **18**, whose optical purity is determined to be 77% ee by HPLC analysis[17] ($[\alpha]^{25}_D$ +126° (*c* 1.44, CCl_4)),[18] gave (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl azide (**19**) ($[\alpha]^{26}_D$ +65.5° (*c* 2.45, $CHCl_3$)) in 80% yield as a single product with the retention of configuration (Scheme II). The absolute configuration of the allyl azide **19** was determined to be *R* by converting it to the known (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-ylamine (**39**) ($[\alpha]^{23}_D$ +10.3° (*c* 4.40, benzene)).[19] The enantiomeric excess of **39** was determined to be 76.4% ee by HPLC analysis of (*R*)-(+)-*N*-[(*E*)-4-phenyl-3-buten-2-yl]benzamide (**40**), which was obtained upon treatment of **39** with benzoyl chloride (71%). These results clearly show that the azidation of allylic acetates proceeds with net retention of configuration. The azide ion for the palladium-catalyzed reaction seems to be a soft nucleophile, although azide ion is assigned as a borderline nucleophile according to the HSAB principle.[20]

The azidation of optically active (1*R*,5*R*)-carvyl diethyl phosphate (**41**) (90% ee) (*E*:*Z* = 5:95) gave racemic (*Z*)-azide **43** (*E*:*Z* = 10:90) (eq 6). The loss of enantiomeric

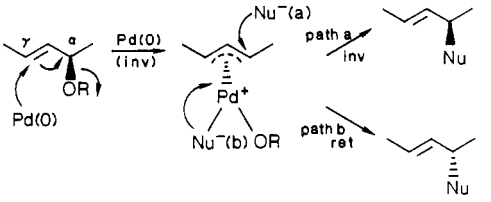


(6)

1*R*,5*R* **41**: R = P(O)(OEt)$_2$ **42**: R = $COCH_3$ 1*R**,5*R** **43**

purity is due to the formation of a symmetric (π-allyl)-palladium intermediate and the facile 1,3-rearrangement of the product azide.[21] The azidation of the corresponding (1*R*,5*R*)-carvyl acetate (**42**) also gave the azide **43**, with a lower *E*:*Z* ratio (25:75).

Scheme III



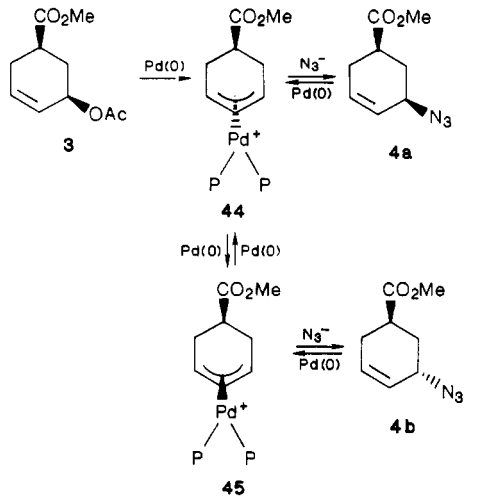
The kinetic resolution of racemic allyl acetates was attempted so far in vain by using an optically active bidentate phosphine. Typically, the reaction of racemic allyl acetate **18** with sodium azide (0.5 equiv) in the presence of $Pd_2(dba)_3$·$CHCl_3$ and (*R*)-(*S*)-BPPFA[22] at 40 °C gave (*S*)-(*E*)-allyl azide **19** (50% yield) and (*R*)-(*E*)-allyl acetate **18** (31% yield) in 2.0 and 3.4% ee, respectively.

Mechanism

Palladium-catalyzed reactions of allylic substitution can be rationalized by assuming Scheme III. Oxidative addition of allyl esters to Pd(0) species gives (π-allyl)palladium intermediates, which react with various nucleophiles to give allyl compounds. The $Pd(PPh_3)_4$-catalyzed azidation of **3** gives **4a** and **4b** without isomerization of the starting **3** under the reaction conditions. The azidations of geranyl and neryl acetates proceed more slowly than that of linalyl acetate, indicating that the oxidative addition of allyl acetates to Pd(0) species occurs at the γ-position.[23] Usually, the oxidative addition of allyl acetates to Pd(0) catalyst proceeds with inversion of configuration at the allylic carbon to give (π-allyl)palladium complexes, which undergo subsequent reactions with nucleophiles such as $^-CH(CO_2R)_2$ and secondary amines with inversion of configuration (path a).[24a-f] In contrast, nucleophiles such as H^- attack initially at palladium, and subsequent migration and reductive elimination result in inversion of configuration (path b).[24g-i] The above stereochemical results of the azidation with $Pd_2(dba)_3$·$CHCl_3$–dppb catalyst are retention of configuration, indicating that the present azidation proceeds via path a. As shown in the reaction of **3**, the addition of a bidentate ligand such as dppb raised the stereoselectivity of the formation of **4a** (38:62 → 91:9). The loss of stereochemistry is due to the isomerization between anti and syn (π-allyl)palladium complexes (**44** and **45**). The isomerization of the (π-allyl)palladium complex bearing monodentate PPh_3 proceeds faster than that bearing bidentate dppb. The azidation of **3** with $Pd_2(dba)_3$·$CHCl_3$–dppb catalyst gave **4a** exclusively; however, the higher concentration of the palladium catalyst decreased the selectivity of **4a**:**4b**. Actually, the ratio of **4a**:**4b** changed as follows: 96:4, 84:16, 83:17, 76:24 in the order of the concentration of the palladium catalyst 1%, 5%, 10%, 20%, respectively. Apparently the isomerization is induced by the palladium(0) catalyst. This result is consistent with the reported result that the optical yields of the asymmetric transformation of allyl carbonates are dependent on the concentration of Pd(0) species, and

(17) Okamoto, Y.; Kawashima, M.; Hatada, K. *J. Chromatogr.* **1986**, *363*, 173.
(18) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723.
(19) (a) Yamamoto, Y.; Oda, J.; Inoue, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3744. (b) Yamamoto, Y.; Oda, J.; Inoue, Y. *J. Org. Chem.* **1976**, *41*, 303.
(20) (a) Pearson, R. G. *Symmetry Rules for Chemical Reactions*; John Wiley: New York, 1976. (b) Ho, T. L. *Chem. Rev.* **1975**, *75*, 1.
(21) Kaboré, I. Z.; Khuong-Huu, Q.; Pancrazi, A. *Tetrahedron* **1978**, *34*, 2807 and 2815.
(22) Hayashi, T.; Yamamoto, A.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1090.
(23) Osakada, K.; Chiba, T.; Nakamura, Y.; Yamamoto, T.; Yamamoto, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1589.
(24) (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Trost, B. M.; Verhoeven, T. R. *Compr. Organomet. Chem.* **1982**, *8*, 799. (c) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer Verlag: Berlin, 1980. (d) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1769. (e) Fiaud, J.-C.; Legros, J.-Y. *J. Org. Chem.* **1987**, *52*, 1907. (f) Onoue, H.; Moritani, I.; Murahashi, S.-I. *Tetrahedron Lett.* **1973**, 121. (g) Hayashi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* **1981**, *22*, 2629. (h) Matsushita, H.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1982**, 160. (i) Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1982**, *23*, 241.

higher concentration results in low asymmetric transformation.[25]



It is noteworthy that the stereochemical isomerization of allyl azides takes place in the presence of palladium cattalyst. Thus, the treatment of azide **4b** with $Pd(PPh_3)_4$ catalyst under similar reaction conditions gave a mixture of azides **4a** and **4b** (38:62). Furthermore, the addition of an excess of PPh_3 decreased the yield of allyl azides. This is due to the formation of iminophosphoranes from allyl azides and phosphines.[26] The palladium(0)-catalyzed isomerization of **4b** proceeds relatively fast, when $Pd(PPh_3)_4$ is used. Thus, the treatment of **4b** with 5 mol % of $Pd(PPh_3)_4$ at 40 °C gave an equilibrated mixture of **4a** and **4b** (35:65) within 1 h. However, when 2.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$–dppb was used, the isomerization of **4b** did not occur even for 2 h. Probably, the palladium(0)-induced isomerization of (π-allyl)palladium species with bidentate ligands proceeds very slowly.

Synthesis of Primary Allylamines

The synthesis of primary allylamines is important;[2,3] however, there is no general method for the synthesis of these compounds. An attractive method is the reduction of allyl azides. Catalytic hydrogenation of allyl azides over palladium catalyst has been used;[27] however, the reduction of the carbon–carbon double bonds often lowers the selectivity. Among various reducing reagents, a combination of PPh_3/NaOH[28] seems to be the most efficient for the synthesis of primary allylamines. The intermediate iminophosphoranes can be used as key intermediates for various nitrogen compounds, such as amides,[29] imines,[30] nitro compounds,[31] and secondary amines.[32]

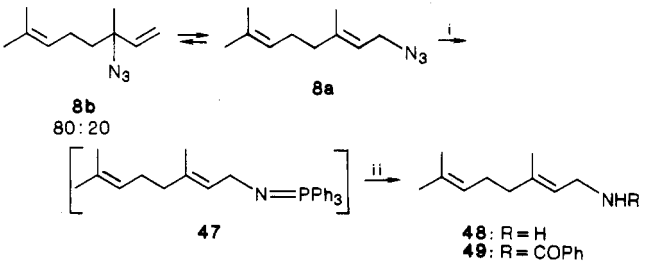
(25) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921.
(26) For a review: Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437.
(27) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590.
(28) Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763.
(29) (a) Garcia, J.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1984**, *25*, 4841. (b) Garcia, J.; Vilarrasa, J.; Bordas, X.; Banaszek, A. *Tetrahedron Lett.* **1986**, *27*, 639. (c) Kusumoto, S.; Sakai, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1296.
(30) (a) Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Chem. Soc., Chem. Commun.* **1982**, 1224. (b) Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Org. Chem.* **1985**, *50*, 5352. (c) Tsuge, O.; Kanemasa, S.; Matsuda, K. *J. Org. Chem.* **1984**, *49*, 2688.
(31) Corey, E. J.; Samuelsson, B.; Luzzio, F. A. *J. Am. Chem. Soc.* **1984**, *106*, 3682.
(32) Zimmer, H.; Jayawant, M.; Gutsch, P. *J. Org. Chem.* **1970**, *35*, 2826.

Table IV. The Phosphine Effect on the Reduction of Octenyl Azides[a]

entry	PR_3	conv,[b] %	yield of **46**,[c] %	ratio[d] **46a:46b**
1	$P(OMe)_3$	11	0	
2	$P(OEt)_3$	49	0	
3	$P(OBu)_3$	44	0	
4	PEt_3	100	98	80:20
5	PBu_3	100	80	75:25
6	PPh_3	98	82	80:20
7	PCy_3	95	0 (49)[e]	(95:5)[e]
8	$P(o\text{-Tol})_3$	5	0	

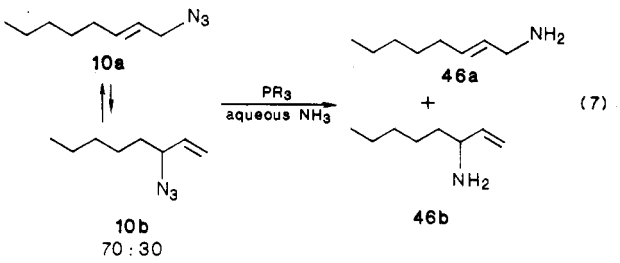
[a] The reactions are similar to the general procedure described in the Experimental Section. [b] Conversions were estimated by the amount of produced nitrogen gas. [c] Isolated yields of allylamines which were obtained by the treatment with ammonium solution. [d] The ratios of **46a:46b** were determined by ^1H NMR analysis. [e] Treatment with 2 N NaOH solution at reflux.

Scheme IV[a]



[a] (i) PPh_3; (ii) NH_4OH.

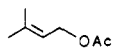
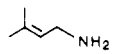
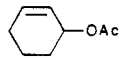
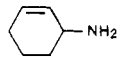
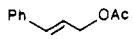
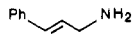
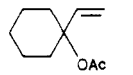
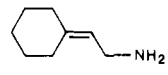
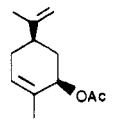
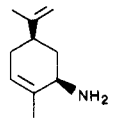
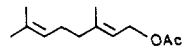
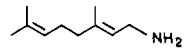
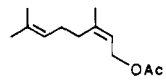
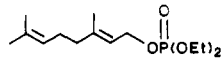
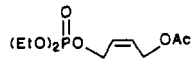
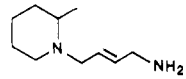
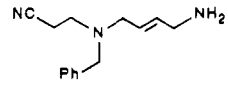
The effect of a phosphine for the reduction of allyl azides has been examined in the case of a mixture of octenyl azides (**10a** and **10b**, 70:30) (eq 7). The mixture was



(7)

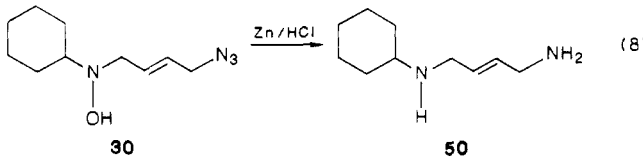
treated with various phosphines at 50 °C for 1 h. The hydrolysis of the iminophosphoranes obtained with aqueous ammonia at 50 °C gave a mixture of 2-octen-1-ylamine (**46a**) and 1-octen-3-ylamine (**46b**). The representative results of the reduction of octenyl azide are shown in Table IV. The conversion of octenyl azide was determined by measuring the amount of nitrogen gas evolved. Phosphites are not effective (entries 1–3) because of low nucleophilicity. The formation of iminophosphoranes proceeds fast upon treatment with nucleophilic phosphines, although the reactivity decreases with increase of the bulkiness of phosphines (entries 7 and 8). The regioselectivity of the reduction of allyl azides is effected by steric bulkiness of phosphines. The reduction of octenyl azide with tricyclohexylphosphine proceeds highly regioselectively (95:5) in comparison with other phosphines (entry 7), although the hydrolysis of iminophosphoranes requires severe reaction conditions. Importantly, less hindered primary amines can be prepared selectively from allyl azides upon treatment with triphenylphosphine and a hydroxide solution. Typically, the treatment of an equilibrated mixture of geranyl (**8a**) and linalyl azide (**8b**) (80:20) with triphenylphosphine gave triphenyl(*N*-geranylimino)phosphorane (**47**) selectively, and hence geranylamine (**48**) was obtained exclusively.

Table V. One-Pot Preparation of Primary Allylamines from Allyl Esters[a]

entry	allyl ester	allylamine	yield,[b] %
1		 **51**	61[c]
2		 **52**	70[c]
3	 **14**	 **53**	59
4		 **54**	80
5	 **42**	 **55**	91
6	 **5**	 **48**	59
7	 **7**	48	62
8	 **12**	48	85[d]
9	 **24**	 **57**	84
10	**24**	 **58**	81

[a] The reactions are similar to the general procedure described in the Experimental Section. [b] Isolated yield. [c] Isolated as amine hydrochloride. [d] Room temperature, 2 h.

The selective formation of **47** is rationalized by assuming that less hindered **8a** reacts with triphenylphosphine much faster than the equilibrated isomer **8b** (Scheme IV). The transformation of optically active azide **21** to amine **39** can be performed with retention of configuration. The reduction of allyl azides is also performed efficiently by using zinc powder. Thus, the treatment of 4-(*N*-cyclohexyl-*N*-hydroxyamino)-2-buten-1-yl azide (**30**) with zinc powder in an aqueous HCl solution gave 4-(*N*-cyclohexylamino)-2-buten-1-ylamine (**50**) in 72% yield (eq 8).[10]

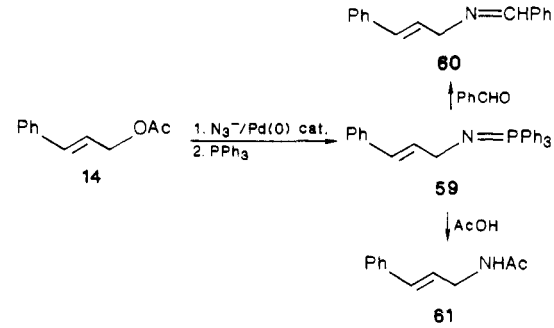


30 **50** (8)

One-Pot Synthesis of Primary Allylamines from Allylic Esters

Allylic acetates can be converted into primary allylamines without isolation of allyl azides upon treatment with triphenylphosphine and subsequently with aqueous ammonia solution. The representative results are listed in Table V. Primary allylamines are obtained selectively regardless of a regioisomeric mixture of allyl azides (entries 4 and 6–8). (1*R*,5*R*)-Carvyl acetate (**42**) can be converted into (1*R**,5*R**)-carvylamine (**55**) selectively with retention of configuration. The stereochemistry of **55** was determined to be 1*R**,5*R** by converting it to the known *N*-((1*R**,5*R**)-carvyl)benzamide (**56**).[33] Allyl phosphates also can be converted into allylamines under mild conditions (entry 8). The sequential amination of 4-acetoxy-2-buten-1-yl phosphate **24** is highly useful for the synthesis of substituted primary (*E*)-allyldiamines. The precursor of spermine alkaloids can be also prepared (entries 9 and 10).

Scheme V



Synthetic Application of Allyl Azides

Allyl azides thus obtained can be readily converted into various nitrogen-containing allylic compounds via iminophosphoranes. Staudinger reaction[26,30] of (*N*-cinnamylimino)triphenylphosphorane (**59**) with benzaldehyde in benzene at reflux gave *N*-benzylidenecinnamylamine (**60**) in >99% yield. The reaction of **59** with acetic acid in benzene at reflux afforded *N*-cinnamylacetamide (**61**) in 57% yield (Scheme V).[29] Interestingly, the reaction of a mixture of geranyl azide and linalyl azide (80:20) with PPh_3 followed by treatment with benzoic acid gave *N*-geranylbenzamide (**49**) selectively in 98% yield.

γ-Amino acids can be prepared by using the present method. (*Z*)-3-Aminocyclohexanecarboxylic acid (**62**), which has anticonvulsant activity,[34] and the amino acid **63** have been prepared by catalytic hydrogenation of the corresponding azido carbyxlic acids **36a** and **36b** in quantitative yields, respectively (Scheme VI).

Conclusion

The palladium-catalyzed azidation provides an efficient method for the transformation of allyl esters into the corresponding allyl azides with *net retention* of configuration. High stereoselectivity is attained by using a low concentration of palladium(0) catalyst and a chelating bidentate ligand, dppb. The allyl azides thus obtained can be readily converted into the corresponding primary allylamines highly selectively upon treatment with triphenylphosphine and subsequently aqueous ammonium solution.

Experimental Section

General. NMR spectra were recorded on JEOL PMX-60-SI (60 MHz), JEOL JNM-FX-100 (^{1}H NMR at 99.60 MHz, ^{13}C NMR at 25.0 MHz, and ^{31}P NMR at 40.25 MHz), and JEOL JNM-GX-500 (500 MHz) spectrometers. Chemical shifts (δ) are expressed in parts per million relative to tetramethylsilane ($CDCl_3$) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (D_2O). The

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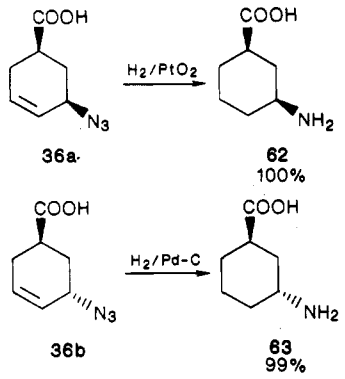
Scheme VI



chemical shifts of ^{31}P NMR spectra are quoted relative to external aqueous 85% phosphoric acid. IR spectra were recorded on a Hitachi 215 spectrometer. Optical rotations were measured with a JASCO DIP-4 polarimeter with 1-dm-long cell at room temperature. GLC analyses were carried out on a Shimadzu GC-9A flame-ionization chromatography by using a 1-m × 3-mm analytical column packed with 10% SE 30 on 80–120 mesh Uniport HP and a Shimadzu GC-mini 2 flame-ionization chromatography by using a 25-m × 0.25-mm PEG 20M chemically bonded on a glass capillary column (Gasukuro Kogyo, Inc., Japan). Mass spectra were obtained on a Shimadzu GCMS QP-1000 by using an analytical column packed with SE 30 on Uniport HP. Elemental analyses were performed on a Yanagimoto MT-3 CHN corder.

CAUTION: Neat azides should be handled carefully behind a safety screen in a hood and stored in a refrigerator. Solutions of azides can be handled with ease.

Materials. THF was distilled over benzophenone ketyl under argon. Water was degassed with argon prior to use. Trimethylsilyl azide,[35] $Pd(PPh_3)_4$,[36] $Pd(dba)_2$,[37] $Pd_2(dba)_3{\cdot}CHCl_3$,[37] $Pd(acac)_2$,[38] $Pd[P(C_6H_{11})_3]_2$,[39] $Pd(OAc)_2$,[40] and $Pd(OCOCF_3)_2$[40] were prepared by the literature procedures. (*Z*)-5-(Methoxycarbonyl)-2-cyclohexen-1-yl acetate (**3**),[41] (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl acetate (**18**),[42] 7-oxabicyclo[3.2.1]oct-2-en-6-one (**35**),[43] and (*Z*)-5-(acetoxymethyl)-2-cyclohexen-1-yl acetate (**37**)[44] were prepared by the literature procedures. (1*R*,5*R*)-Carveol was prepared from (*R*)-(−)-Carvone.[45] Other allylic esters were prepared by the general procedures. Diethyl chlorophosphate was purchased from Aldrich Chemical Co.

Preparation of Allyl Diethyl Phosphates. Diethyl chlorophosphate (7.25 g, 42.0 mmol) was added to a solution of an allyl alcohol (40.0 mmol) and pyridine (3.6 mL) in dichloromethane (40 mL) at 0 °C for 5 min. The resulting white slurry was stirred for 2 h at room temperature. The reaction mixture was diluted with ether (70 mL) and was washed successively with a 10% HCl solution (30 mL × 3), saturated $NaHCO_3$ (30 mL × 3), and brine (30 mL). The organic layer was dried over $MgSO_4$. After removal of the solvent in vacuo, distillation or column chromatography gave allyl diethyl phosphates as colorless oils.

(*E*)-Diethyl 2-hexen-1-yl phosphate (1a): bp 110–111 °C (2.0 mmHg); IR (neat) 1270 (P=O, s), 1000 (POC, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.75–1.15 (m, 3 H), 1.15–1.83 (m, 2 H), 1.37 (t, *J* = 6 Hz, 6 H), 1.87–2.30 (m, 2 H), 4.06 (q, *J* = 7 Hz, 2 H), 4.18 (q, *J* = 7 Hz, 2 H), 4.40 (d, *J* = 5 Hz, 1 H), 4.57 (d, *J* = 5 Hz, 1 H), 5.30–6.12 (m, 2 H).

Diethyl geranyl phosphate (12):[46] IR (neat) 1260 (P=O, s), 1000 (POC, s) cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 1.30 (t, *J* = 7 Hz, 6 H), 1.59 (s, 3 H), 1.65 (s, 3 H), 1.70 (s, 3 H), 1.98–2.15 (m, 4 H), 4.08 (q, *J* = 7 Hz, 2 H), 4.16 (q, *J* = 7 Hz, 2 H), 4.37 (d, *J* = 7 Hz, 1 H), 4.48 (d, *J* = 7 Hz, 1 H), 4.84–5.16 (m, 1 H), 5.35 (t, *J* = 7 Hz, 1 H).

(*E*)-Cinnamyl diethyl phosphate (16): IR (neat) 1260 (P=O, s), 1000 (POC, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.33 (t, *J* = 7 Hz, 6 H), 4.10 (q, *J* = 7 Hz, 2 H), 4.18 (q, *J* = 7 Hz, 2 H), 4.48 (d, *J* = 5 Hz, 1 H), 4.60 (d, *J* = 5 Hz, 1 H), 6.30 (dt, *J* = 15 and 5 Hz, 1 H), 6.78 (d, *J* = 15 Hz, 1 H), 7.18–7.63 (m, 5 H).

(*Z*)-Cinnamyl diethyl phosphate (17): IR (neat) 1270 (P=O, s), 1020 (POC, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.35 (t, *J* = 7 Hz, 6 H), 4.10 (q, *J* = 7 Hz, 2 H), 4.18 (q, *J* = 7 Hz, 2 H), 4.83 (d, *J* = 7 Hz, 1 H), 4.96 (d, *J* = 7 Hz, 1 H), 5.96 (dt, *J* = 11 and 7 Hz, 1 H), 6.80 (d, *J* = 11 Hz, 1 H), 7.20–7.74 (m, 5 H).

(*Z*)-4-Acetoxy-2-buten-1-yl Diethyl Phosphate (24). Diethyl chlorophosphate (72.3 mL, 0.50 mol) was added to a solution of (*Z*)-2-butene-1,4-diol (41.2 mL, 0.50 mol) in pyridine (79.1 mL, 2.0 mol) at 0 °C for 1 h. The resulting white slurry was stirred for 30 min at room temperature. Acetic anhydride (56.5 mL, 0.60 mol) was added to the reaction mixture at 0 °C for 10 min. The reaction mixture was diluted with ether (1.0 L) and washed successively with a 10% HCl solution (500 mL × 3), saturated $NaHCO_3$ (500 mL × 3), and brine (500 mL). The organic layer was dried over $MgSO_4$. After removal of the solvent in vacuo, distillation gave phosphate **24** (32.1 g, 24%): bp 135 °C (1.0 mmHg); IR (neat) 1250 (P=O, s), 1020 (POC, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.36 (t, *J* = 7 Hz, 6 H), 2.06 (s, 3 H), 4.08 (q, *J* = 7 Hz, 2 H), 4.16 (q, *J* = 7 Hz, 2 H), 4.49–4.80 (m, 4 H), 5.72 (dt, *J* = 11.2 and 5.2 Hz, 1 H), 5.83 (dt, *J* = 11.2 and 5.1 Hz, 1 H). Anal. Calcd for $C_{10}H_{19}O_6P$: C, 45.11; H, 7.19. Found: C, 44.69; H, 7.14.

(*Z*)-5-(Methoxycarbonyl)-2-cyclohexen-1-yl Diethyl Phosphate (34). Diethyl chlorophosphate (7.25 g, 42.0 mmol) was added to a solution of (*Z*)-methyl 5-hydroxy-3-cyclohexenecarboxylate (6.24 g, 40.0 mmol) and pyridine (79.1 mL, 2.0 mol) in dichloromethane (40 mL) at 0 °C for 1 h. The resulting white slurry was stirred for 30 min at room temperature. The reaction mixture was diluted with ether (70 mL), washed successively with a 10% HCl solution (30 mL × 3), saturated $NaHCO_3$ (30 mL × 3), and brine (30 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to give phosphate **34** as a colorless oil (13.13 g, 100%): IR (neat) 1735 (C=O, s), 1260 (P=O, s), 1000 (POC, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.33 (t, *J* = 6.8 Hz, 3 H), 1.35 (t, *J* = 6.8 Hz, 3 H), 2.85 (ddd, *J* = 12.3, 12.3, and 9.4 Hz, 1 H), 2.15–2.88 (m, 4 H), 3.68 (s, 3 H), 4.06 (q, *J* = 6.8 Hz, 2 H), 4.13 (q, *J* = 6.8 Hz, 2 H), 4.75–5.13 (m, 1 H), 5.60–5.98 (m, 2 H); ^{31}P NMR ($CDCl_3$, 40.25 MHz) δ −1.25 [(*Z*)-phosphate; ≥99%].

A mixture of (*E*)- and (*Z*)-5-(methoxycarbonyl)-2-cyclohexen-1-yl diethyl phosphate was prepared by the similar treatment of a mixture of *E* and *Z* alcohol (*E*:*Z* = 64:36) with diethyl chlorophosphate. The stereoisomeric ratio of the allyl phosphates **34** was determined by ^{31}P NMR spectra. ^{31}P NMR ($CDCl_3$, 40.25 MHz) showed δ −1.53 for the (*E*)-phosphate and δ −1.25 for the (*Z*)-phosphate. The ratio was 64:36.

(1*R*,5*R*)-(−)-Carvyl diethyl phosphate (41):[47] $[\alpha]^{25}_D$ −37.0° (*c* 1.77, $CHCl_3$); IR (neat) 1270 (P=O, s), 1000 (POC, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.32 (t, *J* = 7.2 Hz, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.67–2.60 (m, 11 H), 4.10 (dq, *J* = 7.2 and 2.4 Hz, 2 H), 4.18 (dq, *J* = 7.2 and 2.4 Hz, 2 H), 4.65–4.80 (m, 1 H), 4.80–5.15 (m, 1 H), 5.50–5.77 (m, 2 H). A ^{31}P NMR signal indicated the presence of the (1*S*,5*R*)-phosphate. ^{31}P NMR ($CDCl_3$, 40.25 MHz): δ −0.87 [(1*R*,5*R*)-phosphate; 95%], −1.24

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[(1S,5R)-phosphate; 5%]. Anal. Calcd for $C_{14}H_{25}O_4P$: C, 58.32; H, 8.74. Found: C, 58.70; H, 8.75.

Effect of Leaving Groups for the Azidation of (*E*)-2-Hexen-1-yl Compounds. A mixture of tetrakis(triphenylphosphine)palladium (0.023 g, 0.02 mmol), sodium azide (90%) (0.087 g, 1.2 mmol), (*E*)-2-hexen-1-yl compounds (1.00 mmol), THF (3.0 mL), and water (1.0 mL) was stirred at 40 °C for 30 min under argon. The conversion of allylic compounds and the yield of hexenyl azides **2a,b** were determined by GLC analysis (SE 30 10%, 1 m × 3 mm) using an internal standard (*n*-tridecane and *n*-tetradecane). The conversions of (*E*)-2-hexenyl compounds are as follows: $(EtO)_2PO_2$- (**1a**, 98%), $EtOCO_2$- (**1b**, 100%), CF_3CO_2- (**1c**, 100%), $PhCO_2$- (**1d**, 97%), CH_3CO_2- (**1e**, 23%), PhO- (**1f**, 0%), Et_2N- (**1g**, 0%), Cl- (**1h**, 100%), and Br- (**1i**, 100%).

Catalytic Activity and Solvent Effect on the Azidation of Allyl Acetate 3. A mixture of palladium catalyst (0.025 mmol, 5 mol %), ligand, sodium azide (0.040 g, 0.55 mmol), (*Z*)-5-(methoxycarbonyl)-2-cyclohexen-1-yl acetate (**3**) (0.099 mg, 0.50 mmol), water (0.5 mL), and a solvent (2 mL) was stirred at 50 °C for 2 h under argon. The conversions of allyl acetate **3** and the yields of allyl azides **4a,b** were determined by GLC analysis (glass capillary chemically bonded column with PEG 20M, 25 m × 0.25 mm) using an internal standard (*n*-docosane). The yields and the conversions (yield/conversion %) by using various solvents are as follows: THF (92/95), DME (73/91), DMF (41/73), acetone (47/73), CH_3CN (22/24), and EtOH (23/23). The results for the catalytic activity are listed in Table III.

General Procedure for the Palladium-Catalyzed Azidation of Allylic Esters. A mixture of $Pd(PPh_3)_4$ (0.5–5 mol %), sodium azide (22 mmol), and allylic compound (20 mmol) in THF (50 mL) and water (20 mL) was stirred at 50 °C for 2 h. The reaction mixture was extracted with ether (50 mL × 3). The combined extracts were washed successively with 2 N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure at room temperature gave allyl azides. Column chromatography on SiO_2 gave pure allyl azides. The representative results are listed in Table I.

Azidation of (*E*)-2-Hexen-1-yl Diethyl Phosphate (1a). The palladium-catalyzed azidation of **1a** was carried out at room temperature for 4 h. Diethyl ether was used as a solvent in place of THF, because the product azide is volatile. Column chromatography (SiO_2, pentane) gave a mixture of (*E*)-2-hexen-1-yl azide (**2a**) and 1-hexen-3-yl azide (**2b**). The ratio of **2a**:**2b** was determined to be 70:30 by ^1H NMR analysis: IR (neat) 2100 (N_3, s) cm^{-1}. For **2a**: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.92 (t, J = 6.0 Hz, 3 H), 1.14–1.80 (m, 2 H, CH_2), 2.07 (dt, J = 7.0 and 6.5 Hz, 2 H, CH_2), 3.68 (d, J = 5.0 Hz, 2 H, CH_2N_3), 4.93–6.10 (m, 2 H, CH=CH). For **2b**: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.92 (t, J = 6.0 Hz, 3 H, CH_3), 1.14–1.80 (m, 4 H, CH_2), 3.50–4.00 (m, 1 H, CHN_3), 4.93–6.10 (m, 3 H, $CH=CH_2$).

Azidations of Geranyl Acetate (5), Linalyl Acetate (6), Neryl Acetate (7), and Geranyl Diethyl Phosphate (12). A mixture of geranyl azide (**8a**)[48] and linalyl azide (**8b**) was obtained by column chromatography (SiO_2, hexane). The ratio of **8a**:**8b** was determined to be 80:20 by ^1H NMR analysis: IR (neat) 2100 (N_3, s) cm^{-1}. For **8a**: ^1H NMR ($CDCl_3$, 100 MHz) δ 1.35–1.79 (m, 9 H, CH_3), 2.07 (m, 4 H, CH_2), 3.74 (d, J = 7.6 Hz, 2 H, CH_2N_3), 4.94–5.90 (m, 2 H, CH=). For **8b**: ^1H NMR ($CDCl_3$, 100 MHz) δ 1.35–1.79 (m, 9 H, CH_3), 2.07 (m, 4 H, CH_2), 4.94–5.90 (m, 4 H, CH=, $CH=CH_2$). Anal. Calcd for $C_{10}H_{17}N_3$: C, 66.99; H, 9.57; N, 23.44. Found: C, 67.05; H, 9.50; N, 23.15.

Azidation of 1-Octen-3-yl Acetate (9). A mixture of (*E*)-2-octen-1-yl azide (**10a**) and 1-octen-3-yl azide (**10b**) was obtained by column chromatography (SiO_2, hexane). The ratio of **10a**:**10b** was determined to be 70:30 by ^1H NMR analysis: IR (neat) 2100 (N_3, s) cm^{-1}. For **10a**: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.60–2.40 (m, 11 H), 3.47–3.96 (m, 2 H, CH_2N_3), 5.00–6.10 (m, 2 H, CH=CH). For **10b**: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.60–2.40 (m, 11 H), 3.47–3.96 (m, 1 H, CHN_3), 5.00–6.10 (m, 3 H, $CH=CH_2$). Anal. Calcd for $C_8H_{15}N_3$: C, 62.71; H, 9.87; N, 27.43. Found: C, 62.75; H, 9.89; N, 27.34.

(*E*)-5-Nonen-4-yl azide (11): IR (neat) 2090 (N_3, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.90 (t, J = 6.5 Hz, 6 H), 1.10–1.70 (m, 6 H), 2.07 (dt, J = 6.5 and 7.0 Hz, 2 H), 3.77 (dt, J = 7.0 and 7.0 Hz, 1 H), 5.30 (dd, J = 15 and 7.0 Hz, 1 H), 5.74 (dt, J = 15 and 6.5 Hz, 1 H).

2-Cyclohexen-1-yl azide (13):[49] IR (neat) 2095 (N_3, s) cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 1.50–2.40 (m, 6 H), 3.58–4.40 (m, 1 H), 5.43–6.15 (m, 2 H). Anal. Calcd for $C_6H_9N_3$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.81; H, 7.42; N, 33.80.

(*E*)-Cinnamyl azide (15):[50] IR (neat) 2100 (N_3, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 3.85 (d, J = 6.3 Hz, 2 H), 6.16 (dt, J = 15.6 and 6.3 Hz, 1 H), 6.60 (d, J = 15.6 Hz, 1 H), 7.19–7.38 (m, 5 H). Anal. Calcd for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.03; H, 5.71; N, 26.28.

(*R*)-(*E*)-(+)-4-Phenyl-3-buten-2-yl azide (19): $[\alpha]^{26}_D$ +65.5° (*c* 2.45, $CHCl_3$); IR (neat) 2100 (N_3, s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 6.5 Hz, 3 H, Me), 4.10 (dq, J = 6.5 and 6.5 Hz, 1 H, CH), 6.07 (dd, J = 15.5 and 6.5 Hz, 1 H, CH=), 6.60 (d, J = 15.5 Hz, 1 H, CH=), 7.05–7.55 (m, 5 H, Ar H).

(*E*)-1,3-Diphenylallyl azide (20): IR (neat) 2100 (N_3, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.13 (d, J = 6.5 Hz, 1 H), 6.22 (dd, J = 15.5 and 6.5 Hz, 1 H), 6.70 (d, J = 15.5 Hz, 1 H), 7.10–7.60 (m, 5 H).

(*E*)-Methyl 4-azido-2-butenoate (21): IR (neat) 2100 (N_3, s), 1730 (C=O, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.78 (s, 3 H, CH_3), 4.00 (dt, J = 5.0 and 1.5 Hz, 2 H, CH_2), 6.05 (dt, J = 15 and 1.5 Hz, 1 H, CH=), 6.88 (dt, J = 15 and 5.0 Hz, 1 H, CH=). Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.47; H, 4.92; N, 29.84.

(*E*)-Methyl 4-azido-2-pentenoate (22): IR (neat) 2100 (N_3, s), 1720 (C=O, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.35 (d, J = 7.0 Hz, 3 H), 3.75 (s, 3 H), 4.13 (dq, J = 7.0 and 6.5 Hz, 1 H), 5.93 (dd, J = 15 and 1.3 Hz, 1 H), 6.78 (dd, J = 15 and 6.5 Hz, 1 H).

(*E*)-4-Azido-2-pentenenitrile (23): IR (neat) 2100 (N_3, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.37 (d, J = 7.0 Hz, 3 H), 4.22 (dq, J = 7.0 and 6.5 Hz, 1 H), 5.55 (dd, J = 16 and 1.3 Hz, 1 H), 6.57 (dd, J = 16 and 5.5 Hz, 1 H).

Azidation of (*Z*)-4-Acetoxy-2-buten-1-yl Diethyl Phosphate (24). A mixture of (*E*)-4-azido-2-buten-1-yl acetate (**25a**) and 2-azido-3-buten-1-yl acetate (**25b**) was obtained by column chromatography (SiO_2, ethyl acetate:hexane = 1:5). The ratio of **25a**:**25b** was determined to be 80:20 by ^1H NMR analysis: IR (neat) 2105 (N_3, s), 1745 (C=O, s) cm^{-1}. For **25a**: ^1H NMR ($CDCl_3$, 100 MHz) δ 2.07 (s, 3 H), 3.78 (d, J = 4.7 Hz, 2 H, CH_2N_3), 4.55 (d, J = 4.8 Hz, 2 H, CH_2OAc), 5.71 (dt, J = 15 and 4.8 Hz, 1 H, CH=), 5.87 (dt, J = 15 and 4.7 Hz, 1 H, CH=). For **25b**: ^1H NMR ($CDCl_3$, 100 MHz) δ 2.07 (s, 3 H, CH_3CO), 4.00–4.23 (m, 1 H, CHN_3), 5.24–5.66 (m, 3 H, $CH=CH_2$).

Azidation of Cinnamyl Diethyl Phosphate (16) with $TMSN_3$/Bu_4NF. To a solution of $Pd(PPh_3)_4$ (0.024 g, 0.02 mmol) in THF were successively added cinnamyl diethyl phosphate (**16**) (0.540 g, 2.00 mmol), trimethylsilyl azide (0.131 g, 2.00 mmol), and a 1 M solution of Bu_4NF in THF (2.0 mL, 2.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h. To the reaction mixture was added $Ca(OH)_2$. The reaction mixture was diluted with ether (50 mL) and washed with 10% $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Short-column chromatography (SiO_2, benzene) gave cinnamyl azide (**15**) (0.270 g, 85%).

(*Z*)-5-(Acetoxymethyl)-2-cyclohexen-1-yl Azide (38). The azidation of (*Z*)-5-(acetoxymethyl)-2-cyclohexenyl acetate (**37**) (*Z*:*E* = 96:4) was carried out at 50 °C for 2 h by using $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %) and dppb (10 mol %). Azide **38** was obtained in 90% (*Z*:*E* = 93:7) yield. The ratio of **38** was determined by GLC analysis: IR (neat) 2095 (N_3, s), 1740 (C=O, s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.36 (ddd, J = 12.4, 12.4, and 10.5 Hz, 1 H), 1.79–1.87 (m, 1 H), 2.00–2.17 (m, 3 H), 2.06 (s, 3 H), 3.98 (dd, J = 11.0 and 6.4 Hz, 1 H), 4.02 (dd, J = 11.0 and 6.4 Hz, 1 H), 3.95–4.02 (m, 1 H), 5.67 (dm, J = 5.6 Hz, 1 H), 5.90 (dddd, J = 7.6, 5.0, 5.0, and 2.5 Hz, 1 H).

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(1*R,5*R**)-*p*-1,8-Menthadien-6-yl Azide (Carvyl Azide) (43).**[21] The azidations of carvyl diethyl phosphate (41) and carvyl acetate (42) were carried out at 60 °C for 3 h using $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %) and dppb (10 mol %). Carvyl azide was obtained in 59% (1*S**,5*R**:1*R**,5*R** = 10:90) and 49% (1*S**,5*R**:1*R**,5*R** = 25:75) yield, respectively. The ratio of **43** was determined by GLC analysis: $[\alpha]^{25}_D$ 0° (*c* 10.0, $CHCl_3$); IR (neat) 2100 (N_3, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.50–2.50 (m, 11 H), 3.57–3.83 (m, 1 H), 4.65 (s, 2 H), 5.39–5.75 (m, 1 H). Anal. Calcd for $C_{10}H_{15}N_3$: C, 67.76; H, 8.53; N, 23.71. Found: C, 68.10; H, 8.52; N, 23.38.

(*Z*)-5-Azido-3-cyclohexenecarboxylic Acid (36a). To a solution of palladium acetate (0.179 g, 0.800 mmol), triphenylphosphine (0.420 g, 1.60 mmol), and sodium azide (90%) (1.59 g, 22.0 mmol) in THF (50 mL) were added 7-oxabicyclo[3.2.1]-oct-2-en-6-one (**35**) (2.48 g, 20.0 mmol) and water (20 mL) with stirring. After additional stirring at 50 °C for 2 h, most of the organic solvent was removed, and to the resulting aqueous residue were added 2 N NaOH (20 mL) and benzene (30 mL). The mixture was washed with benzene (30 mL × 2) and ether (30 mL). The combined aqueous layer was acidified with a concentrated HCl solution below 10 °C. The acidic phase was extracted with CH_2Cl_2 (30 mL × 3). The combined extracts were dried over Na_2SO_4 and evapoorated to give acid **36a** as a white solid (3.08 g, 92%). An analytical sample was obtained by recrystallization from ether/pentane: mp 69–75 °C; IR (KBr) 2870 (COOH, s), 2070 (N_3, s), 1690 (C=O, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.40–3.10 (m, 5 H), 3.75–4.30 (m, 1 H), 5.45–6.25 (m, 2 H), 10.95 (s, 1 H). Anal. Calcd for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.35; H, 5.42; N, 25.07.

(*E*)-5-Azido-3-cyclohexenecarboxylic Acid (36b). As described above, the reaction of lactone **35** (0.248 g, 2.00 mmol) with sodium azide (90%) (0.159 g, 2.20 mmol) in THF (5 mL) and water (2 mL) was carried out at 50 °C for 2 days in the absence of palladium catalysis. Workup and purification as previously described afforded **36b** (0.278 g, 83%). An analytical sample was recrystallized from ether/pentane: mp 50–51 °C; IR (KBr) 2870 (COOH, br s), 2100 (N_3, s), 1685 (C=O, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.85 (ddd, *J* = 13.6, 12.0, and 4.0 Hz, 1 H), 2.15 (dm, *J* = 13.6 Hz, 1 H), 2.28–2.43 (m, 2 H), 2.79 (dddd, *J* = 12.2, 9.6, 5.7, and 3.2 Hz, 1 H), 3.85–4.14 (m, 1 H), 5.77 (dm, *J* = 5.0 Hz, 1 H), 6.02 (dm, *J* = 5.0 Hz, 1 H), 11.20 (s, 1 H).

(*Z*)-Methyl 5-Azido-3-cyclohexenecarboxylate (4a). To a solution of azido carboxylic acid **36a** (0.318 g, 1.90 mmol) in ether (10 mL) was added a solution of diazomethane in ether dropwise at 0 °C until the evolution of nitrogen ceased. The reaction mixture was quenched with acetic acid and washed with a saturated $NaHCO_3$ solution. The ethereal phase was dried over $MgSO_4$ and evaporated. Short-column chromatography on silica gel (ether) gave colorless **4a** (0.306 g, 89%). GLC analysis indicated the presence of the *E* isomer (5%): IR (neat) 2090 (N_3, s), 1740 (C=O, s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.72 (ddd, *J* = 12.6, 12.6, and 10.3 Hz, 1 H), 2.27–2.33 (m, 2 H), 2.34–2.41 (m, 1 H), 2.67 (dddd, *J* = 12.6, 9.28, 6.07, and 2.75 Hz, 1 H), 3.71 (s, 3 H), 3.95–4.03 (m, 1 H), 5.62–5.69 (m, 1 H), 5.88–5.93 (m, 1 H); ^{13}C NMR ($CDCl_3$, 25.0 MHz) δ 26.9, 30.5, 37.9, 51.6, 56.7, 125.6, 129.2, 174.0. Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.10; H, 6.07; N, 23.26. The palladium-catalyzed azidation of allyl acetate **3** or allyl phosphate **34** gave **4a** stereoselectively.

(*E*)-Methyl 5-Azido-3-cyclohexenecarboxylate (4b). The reaction of **36b** (0.278 g, 1.66 mmol) with a solution of diazomethane in ether gave **4b** (0.299 g, 100%). GLC analysis showed the presence of the *Z* isomer (2%): IR (neat) 2090 (N_3, s), 1730 (C=O, s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.90 (ddd, *J* = 13.75, 11.92, and 4.81 Hz, 1 H), 2.13 (ddd, *J* = 13.75, 3.09, and 3.09 Hz, 1 H), 2.24 (dddd, *J* = 18.33, 10.20, 4.59, and 2.52 Hz, 1 H), 2.40 (ddd, *J* = 18.33, 5.16, and 5.16 Hz, 1 H), 2.77 (dddd, *J* = 11.92, 10.08, 5.50, and 3.21 Hz, 1 H), 3.71 (s, 3 H), 4.02 (s, 1 H), 5.80 (ddd, *J* = 9.85, 2.98, and 1.61 Hz, 1 H), 6.04 (dddd, *J* = 9.85, 4.82, 2.75, and 1.14 Hz, 1 H); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 27.3, 30.8, 34.8, 51.7, 54.2, 123.3, 131.2, 174.9. This compound was also obtained from the noncatalyzed azidation of allylic phosphate **34**.

Attempted Palladium(0)-Catalyzed Kinetic Resolution of (*E*)-4-Phenyl-3-buten-2-yl Acetate (18). To a mixture of (*E*)-4-phenyl-3-buten-2-yl acetate (**18**) (0.380 g, 2.00 mmol), sodium azide (72 mg, 1.00 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (10.3 mg, 0.01 mmol), and (*R*)-(*S*)-BPPFA (25.0 mg, 0.04 mmol) in THF (5.0 mL) was added water (2.0 mL). After stirring at 40 °C for 2 h, the reaction mixture was extracted with ether (50 mL) and washed successively with a 2 N HCl solution (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4. Removal of the solvent and column chromatography (SiO_2) of the residue gave (*S*)-(*E*)-allyl azide **19** ($[\alpha]^{23}_D$ −1.39 (*c* 2.52, $CHCl_3$)) (R_f = 0.85, benzene) and (*R*)-(*E*)-allyl acetate **18** ($[\alpha]^{23}_D$ +4.55° (*c* 1.41, CCl_4)) (R_f = 0.45, benzene). The optical yields of **19** and **18** are 2.0% ee and 3.4% ee, respectively.

General Procedure for Sequential Amination and Azidation of (*Z*)-4-Acetoxy-2-buten-1-yl Diethyl Phosphate (24). To a solution of $Pd(PPh_3)_4$ (0.231 g, 0.20 mmol) and **24** (1.33 g, 5.0 mmol) in THF (13 mL) was added an amine dropwise with stirring at room temperature. After additional stirring for 2 h, a solution of sodium azide (90%) (0.361 g, 5.0 mmol) in water (5 mL) was added. The reaction mixture was stirred overnight. The ether extracts (30 mL × 3) were dried over Na_2SO_4 and evaporated. Column chromatography on SiO_2 (benzene) gave an azide. The representative results are listed in Table II.

3-[*N*-[(*E*)-4-Azido-2-buten-1-yl]-*N*-benzylamino]propionitrile (28): IR (neat) 2245 (CN, w), 2100 (N_3, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 2.38 (t, *J* = 4.3 Hz, 2 H), 2.78 (d, *J* = 4.3 Hz, 2 H), 3.16 (d, *J* = 5.0 Hz, 2 H), 3.62 (s, 2 H), 3.73 (d, *J* = 5.0 Hz, 2 H), 5.71 (dt, *J* = 15.3 and 5.0 Hz, 1 H), 5.75 (dt, *J* = 15.3 and 5.0 Hz, 1 H), 7.27 (br, 5 H); mass spectrum, *m/e* (rel %); 255 (12), 215 (100), 173 (57). Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.87; H, 6.70; N, 27.45.

(*E*)-4-(2-Methylpiperidino)-2-butenyl azide (29): IR (neat) 2090 (N_3, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.00 (d, *J* = 6.0 Hz, 3 H), 1.15–3.50 (m, 11 H), 3.67 (d, *J* = 4.5 Hz, 2 H), 5.25–6.20 (m, 2 H). Anal. Calcd for $C_{10}H_{18}N_4$: C, 61.82; H, 9.34; N, 28.84. Found: C, 62.18; H, 9.41; N, 28.23; mass spectrum, *m/e* 194 (M^+).

(*E*)-4-(*N*-Cyclohexyl-*N*-hydroxyamino)-2-butenyl azide (30): ^1H NMR ($CDCl_3$, 60 MHz) δ 0.77–2.67 (m, 10 H), 2.67–2.88 (m, 1 H), 3.45 (d, *J* = 4.5 Hz, 2 H), 3.75 (d, *J* = 5 Hz, 2 H), 5.03–6.67 (br, 1 H), 5.62 (dt, *J* = 15 and 4.5 Hz, 1 H), 5.98 (dt, *J* = 15 and 5 Hz, 1 H).

General Procedure for Sequential Alkylation and Azidation of (*Z*)-4-Acetoxy-2-butenyl Diethyl Phosphate (24). To a solution of $Pd(PPh_3)_4$ (0.231 g, 0.20 mmol) and **24** (1.330 g, 5.0 mmol) in THF (10 mL) was added alkyl sodium (5.0 mmol) in THF (10 mL) slowly with stirring at 0 °C. After additional stirring for 2 h, a solution of sodium azide (90%) (0.361 g, 5.0 mmol) in water (5 mL) was added. The reaction mixture was stirred overnight. The ether extracts (30 mL × 3) were dried over Na_2SO_4 and evaporated. The allyl azide was purified by column chromatography (SiO_2). The results are listed in Table II.

Methyl (*E*)-2-(phenylsulfonyl)-6-azido-4-hexenoate (31): IR (neat) 2105 (N_3, s), 1745 (C=O, s), 1330 (SO_2, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 2.60–3.00 (m, 2 H), 3.50–4.10 (m, 6 H), 5.40–5.84 (m, 2 H), 7.47–8.00 (m, 5 H).

Ethyl (*E*)-2-cyano-6-azido-4-hexenoate (32): IR (neat) 2270 (CN, w), 2105 (N_3, s), 1745 (C=O, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.30 (t, *J* = 7.0 Hz, 3 H), 2.57–2.77 (m, 2 H), 3.43 (s, 1 H), 3.84 (d, *J* = 3.5 Hz, 2 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 5.35–6.07 (m, 2 H).

Methyl (*E*)-2-(methoxycarbonyl)-6-azido-4-hexenoate (33): IR (neat) 2100 (N_3, s), 1750 (C=O, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 2.67 (dd, *J* = 7.4 and 5.7 Hz, 2 H), 3.45 (t, *J* = 7.4 Hz, 1 H), 3.67 (d, *J* = 5.4 Hz, 2 H), 3.72 (s, 6 H), 5.58 (dt, *J* = 15 and 5.4 Hz, 1 H), 5.72 (dt, *J* = 15 and 5.7, 1 H). Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.81; H, 5.73; N, 18.88.

General Procedure for the Preparation of Primary Allylamines from Allyl Azides: Effects of Phosphine. To a solution of a phosphine (2.20 mmol) in THF (5 mL) was added a mixture of octenyl azides **10a** and **10b** (0.307 g, 2.00 mmol) with stirring at 50 °C, and the reaction mixture was stirred at 50 °C for 1 h. The conversion of allyl azides **10a,b** was determined by measuring the volume of nitrogen evolution. After aqueous ammonia (28%, 5 mL) was added, the reaction mixture was stirred at 50 °C for 1.5 h and was extracted with ether (30 mL × 3). The ether extracts were extracted with a 2 N HCl (10 mL × 3) solution.

The aqueous layer was washed with benzene (10 mL) and made strongly alkaline with a NaOH pellet. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated to give a mixture of (*E*)-2-octen-1-ylamine (**46a**) and 1-octen-3-ylamine (**46b**). The results of using various phosphines and phosphites are listed in Table IV.

General Procedure for the Preparation of Primary Allylamines from Allyl Azides. To a solution of allyl azide (2.0 mmol) in THF (10 mL) was added PPh_3 (2.2 mmol) at room temperature. After the solution was stirred at 50 °C for 2 h, a 2 N NaOH solution (10 mL) or 30% aqueous ammonia (5 mL) was added. The reaction mixture was extracted with ether (30 mL × 3). The organic layer was extracted with a 2 N HCl (10 mL × 3) solution. The aqueous layer was washed with benzene (10 mL) and made strongly alkaline with NaOH. The CH_2Cl_2 extracts (10 mL × 3) were dried over $MgSO_4$. Distillation gave pure allylamines.

(*R*)-(*E*)-(+)-4-Phenyl-3-buten-2-ylamine (39): $[\alpha]^{23}_D$ +10.3° (*c* 4.4, benzene) (lit.[19] *S*-form $[\alpha]^{25}_D$ −8.9° (*c* 10.0, benzene)); IR (neat) 3350 (br, NH) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.20 (d, J = 6.0 Hz, 3 H), 1.45 (br s, 2 H), 3.60 (dq, J = 6.0 and 6.0 Hz, 1 H), 6.08 (dd, J = 16 and 6.0 Hz, 1 H), 6.45 (d, J = 16 Hz, 1 H), 7.0–7.50 (m, 5 H).

Reaction of Octenyl Azides 10a,b with PPh_3. A mixture of 2-octen-1-ylamine (**46a**)[6] and 1-octen-3-ylamine (**46b**) was obtained. The ratio **46a**:**46b** was determined to be 80:20 by ^1H NMR analysis: bp 59–62 °C (4.0 mmHg) (Kugelrohr); IR (neat) 3270 (NH_2, s) cm^{-1}. The analytical sample was purified by preparative GLC (SE30 10%, 1 m × 3 mm, He). For **46a**: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.88 (t, J = 5 Hz, 3 H), 1.05–1.60 (m, 6 H), 1.75–2.30 (m, 2 H), 3.15–3.40 (m, 2 H), 5.30–5.70 (m, 2 H). For **46b**: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.89 (t, J = 5 Hz, 3 H), 1.10–1.60 (m, 8 H), 3.10–3.50 (m, 1 H), 4.93 (ddd, J = 9.5, 1.2, and 1.2 Hz, 1 H), 5.02 (ddd, J = 16.5, 1.2, and 1.2 Hz, 1 H), 5.80 (ddd, J = 16.5, 9.5, and 6.5 Hz, 1 H). Anal. Calcd for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.15; H, 13.59; N, 11.15.

Reaction of Octenyl Azides 10a,b with PCy_3. A solution of tricyclohexylphosphine in toluene (30.4%, 1.54 g, 5.50 mmol) was evaporated under reduced pressure, and THF (12.5 mL) was added. A mixture of 2-octen-1-yl azide (**10a**) and 1-octen-3-yl azide (**10b**) (0.766 g, 5.00 mmol) was added, and the mixture was stirred at 60 °C for 1 h. Then a 2 N NaOH solution (15 mL) was added to the reaction mixture. The mixture was refluxed for 5 h. Isolation of amine **46** was carried out as described above. Kugelrohr distillation gave allylamine **46** (0.310 g, 49%): bp 59 °C (4 mmHg). The ratio of **46a** and **46b** was determined to be 95:5 by ^1H NMR analysis as described above.

Geranylamine (48): bp 50–60 °C (0.15 mmHg) [lit.[48,51] bp 62–65 °C (1.0 mmHg)] (Kugelrohr); IR (neat) 3360 (NH_2, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.18 (s, 2 H), 1.30–2.30 (m, 13 H), 3.23 (d, J = 7.0 Hz, 2 H), 4.80–5.48 (m, 2 H). Anal. Calcd for $C_{10}H_{19}N$: C, 78.36; H, 12.50, N, 9.14. Found: C, 78.21; H, 12.45; N, 8.98.

Cinnamylamine (53):[27,50] IR (neat) 3360 (NH, br), 3280 (NH, br) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.13 (s, 2 H), 3.40 (d, J = 4 Hz, 2 H), 5.90–6.70 (m, 2 H), 7.05–7.60 (m, 5 H).

General Procedure for One-Pot Preparation of Primary Allylamines from Allyl Esters. To a solution of $Pd(PPh_3)_4$ (0.116 g, 0.1 mmol) and an allylic acetate (2.0 mmol) in THF (6 mL) was added a solution of sodium azide (90%) (0.144 g, 2.0 mmol) in water (2 mL), and the mixture was stirred at 50 °C for 2 h. To the reaction mixture was added PPh_3 (0.576 g, 2.2 mmol). After additional stirring at 50 °C for 2 h, a 2 N NaOH solution (10 mL) was added, and the mixture was stirred at 50 °C for 1 h. The ethereal layer (30 mL × 3) was extracted with a 2 N HCl solution (10 mL × 3). The aqueous layer was washed with benzene (10 mL), made strongly alkaline with NaOH, and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated to give allylamine. The results are summarized in Table V.

3-Methyl-2-butenylamine hydrochloride (51): mp 196–198 °C (lit.[52] mp 201 °C); ^1H NMR (D_2O, 60 MHz) δ 1.90–2.50 (m, 6 H), 4.03 (d, J = 7.0 Hz, 2 H), 5.65 (tq, J = 7.0 and 1.2 Hz, 1 H).

2-Cyclohexenylamine hydrochloride (52):[53] mp 156–157 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.10–2.70 (m, 6 H), 3.50–4.20 (m, 1 H), 0.59–6.30 (m, 2 H), 7.50–9.50 (m, 3 H). Anal. Calcd for $C_6H_{12}NCl$: C, 53.93; H, 9.05; N, 10.48. Found: C, 53.81; H, 8.98; N, 10.44.

2-Cyclohexylidenethylamine (54): IR (neat) 3360 (NH_2, br s), 3270 (NH_2, br s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.22 (s, 2 H), 1.36–1.80 (m, 6 H), 1.85–2.36 (m, 4 H), 3.22 (d, J = 7 Hz, 2 H), 5.18 (t, J = 7 Hz, 1 H).

(1*R,5*R**)-*p*-1,8-Menthadien-6-ylamine (carvylamine) (55):**[21] IR (neat) 3200 (br, NH); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.48 (s, 2 H), 1.50–2.50 (m, 11 H), 3.18 (t, J = 3.5 Hz, 1 H), 4.68 (s, 2 H), 5.25–5.58 (m, 1 H).

(*E*)-4-(2-Methylpiperidino)-2-butenylamine (57): bp 79–83 °C (0.4 mmHg) (Kugelrohr); IR (neat) 3270 (NH_2, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.07 (d, J = 7.0 Hz, 3 H) 1.14–1.85 (m, 9 H), 1.85–2.45 (m, 2 H), 2.67–3.06 (m, 2 H), 3.14–3.47 (m, 2 H), 5.64 (dt, J = 16.0 and 4.7 Hz, 1 H), 5.65 (dt, J = 16.0 and 4.7 Hz, 1 H). Anal. Calcd for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.65. Found: C, 71.18; H, 11.94; N, 16.70; mass spectrum, *m/e* (rel %) 168 (5), 153 (100), 136 (36).

3-[*N*-[(*E*)-4-Amino-2-buten-1-yl]-*N*-benzylamino]propionitrile (58): IR (neat) 3300 (NH_2, s), 2250 (CN, w) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.59 (br, 2 H), 2.39 (d, J = 6.0 Hz, 2 H), 2.68 (d, J = 6.0 Hz, 2 H), 2.92–3.34 (m, 4 H), 3.57 (s, 2 H), 5.35–6.01 (m, 2 H), 7.21 (br, 5 H).

(*E*)-4-(*N*-Cyclohexylamino)-2-buten-1-ylamine (50).[10] A mixture of azide **30** (0.183 g, 0.870 mmol) and zinc powder (0.285 g, 4.35 mmol) in 6 N HCl (6 mL) was heated at 80 °C for 2 h with stirring. The reaction mixture was washed with ether (20 mL × 2). The aqueous layer was made alkaline with a 6 N NaOH solution, reextracted with CH_2Cl_2, and dried over K_2CO_3. Evaporation of the filtrate gave diamine **50** (0.105 g, 72%): ^1H NMR ($CDCl_3$, 60 MHz) δ 0.83–2.80 (m, 13 H), 3.17–3.47 (m, 4 H), 5.20–6.03 (m, 2 H).

Preparation of *N*-Allylimines. *N*-Benzylidenecinnamylamine (60). To a solution of cinnamyl azide (**15**) (0.159 g, 1.0 mmol) and benzaldehyde (0.106 g, 1.0 mmol) in dry benzene (5 mL) was added PPh_3 (0.262 g, 1.0 mmol). The solution was refluxed for 2 h. After removal of the solvent, the residue was triturated with dry hexane (10 mL). The solid that precipitated (triphenylphosphine oxide) was removed by filtration. Concentration gave imine **60** (0.228 g, 100%): ^1H NMR ($CDCl_3$, 60 MHz) δ 4.42 (d, J = 4.0 Hz, 2 H), 6.10–6.90 (m, 2 H), 7.10–8.15 (m, 10 H), 8.33 (s, 1 H).

Preparation of *N*-Allylamides. (*R*)-(+)-*N*-[(*E*)-4-Phenyl-3-buten-2-yl]benzamide (40). To a soltuion of (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-ylamine (**39**) (0.103 g, 0.70 mmol) in CH_2Cl_2 (1.5 mL) was added triethylamine (0.7 mL). Benzoyl chloride (93 μL, 0.80 mmol) was added to the solution slowly. The resulting slurry was stirred for 10 h at room temperature. The mixture was diluted with ether (20 mL) and washed successively with a 2 N HCl solution (5 mL × 2), saturated $NaHCO_3$ (5 mL), and brine (5 mL). Evaporation gave a yellow solid. Column chromatography (SiO_2, CH_2Cl_2/hexane) gave allylamide (0.125 g, 71%). The optical purity of amide **40** was determined to be 76.4% ee by HPLC analysis using a chiral column:[17] $[\alpha]^{23}_D$ +34.8° (*c* 2.44, $CHCl_3$); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.35 (d, J = 6.5 Hz, 3 H, Me), 4.10 (dq, J = 6.5 and 6.5 Hz, 1 H, CH), 5.40–5.80 (br, NH, 1 H), 6.07 (dd, J = 15.5 and 6.5 Hz, 1 H, CH=), 6.60 (d, J = 15.5 Hz, 1 H, CH=), 7.05–7.55 (m, 5 H, Ar).

***N*-Geranylbenzamide (49).** A mixture of geranyl azide (**8a**) and linalyl azide (**8b**) (0.224 g, 12.25 mmol), PPh_3 (0.360 g, 1.38 mmol), and benzoic acid (0.168 g, 1.38 mmol) was allowed to react according to the procedure described above. *N*-Geranylbenzamide (**49**) (0.750 g, 98%) containing triphenylphosphine oxide was obtained. The yield of **49** (98%) was determined by ^1H NMR analysis: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.40–2.30 (m, 13 H), 4.05

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(dd, J = 6.0 and 6.0 Hz, 2 H), 4.70–5.50 (m, 2 H), 6.70 (br, 1 H), 7.00–8.15 (m, 5 H).

***N*-((1*R**,5*R**)-Carvyl)benzamide (56).** To a solution of carvylamine (**55**) (53 mg, 0.35 mmol) in CH_2Cl_2 (2.0 mL) was added triethylamine (0.35 mL). Benzoyl chloride (58 μL) was added to the solution. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with ether (10 mL) and washed with a 2 N HCl solution (5 mL) and saturated $NaHCO_3$ solution (5 mL). The extracts were dried over $MgSO_4$ and evaporated in vacuo. Benzamide **56** was purified by column chromatography (SiO_2, ether). An analytical sample was recrystallized from ether/pentane. Benzamide **56** (79 mg, 90%) was obtained as a colorless solid: mp 167–169 °C (lit.[33] mp 169 °C); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.50–2.55 (m, 11 H), 4.70 (s, 2 H, CH_2=), 4.40–5.03 (m, 1 H, CHN), 5.42–5.82 (m, 1 H, CH=), 5.82–6.70 (br, 1 H, NHCO), 7.13–8.22 (m, 5 H, Ph).

***N*-Cinnamylacetamide (61).**[54] To a solution of cinnamyl azide (**15**) (0.159 g, 1.0 mmol) and acetic acid (0.360 g, 6.0 mmol) in benzene (5 mL) was added PPh_3 (0.262 g, 1.0 mmol). After the solution was heated at reflux for 30 h, saturated $NaHCO_3$ solution (10 mL) was added. The combined benzene extracts (10 mL × 3) were washed with a saturated $NaHCO_3$ solution (10 mL × 3), dried over $MgSO_4$, and evaporated. Preparative TLC (SiO_2, CH_2Cl_2, R_f = 0.14) gave *N*-cinnamylacetamide (**61**) (0.397 g, 57%), which contained triphenylphosphine oxide. The yield was determined by ^1H NMR analysis: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.98 (s, 3 H), 3.90 (d, J = 6.0 Hz, 1 H), 4.00 (d, J = 6.0 Hz, 1 H), 6.07 (dt, J = 16 and 6.0 Hz, 1 H), 6.47 (d, J = 16 Hz, 1 H), 7.05–8.30 (m, 5 H).

Catalytic Hydrogenation of Azido Carboxylic Acids. A suspension of a mixture of azido carboxylic acids (**36a** or **36b**) (0.334 g, 2.00 mmol) and a catalyst in EtOH (5 mL) and water (2 mL) was stirred at room temperature for 2 days under a hydrogen atmosphere. Filtration through a pad of Celite using EtOH and water and evaporation gave an amino acid. Analytically pure samples were obtained by recrystallization ($EtOH/H_2O$).

***(Z)*-3-Aminocyclohexanecarboxylic Acid (62).** PtO_2 (23 mg) was used: quantitative yield (0.286 g, 100%); mp 277.5–278 °C (lit.[34] mp 284 °C); ^1H NMR (D_2O, 500 MHz) δ 1.21–1.49 (m, 4 H), 1.91 (d, J = 15 Hz, 2 H), 2.02 (d, J = 12 Hz, 1 H), 2.18 (d, J = 12 Hz, 1 H), 2.27 (t, J = 13 Hz, 1 H), 3.19–3.28 (m, 1 H). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.24; H, 9.04; N, 9.57.

***(E)*-3-Aminocyclohexanecarboxylic Acid (63).** Five percent Pd/C (34 mg) was used: quantitative yield (0.284 g, 99%); mp 292.5–294 °C (lit.[34] mp 290–291 °C); ^1H NMR (D_2O, 500 MHz) δ 1.48–1.59 (m, 2 H), 1.59–1.67 (m, 2 H), 1.67–1.74 (m, 1 H), 1.75–1.83 (m, 1 H), 1.86–1.95 (m, 1 H), 2.09–2.17 (m, 1 H), 2.56–.264 (m, 1 H), 3.48–3.55 (m, 1 H). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.36; H, 9.00; N, 9.66.

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Reductive Lactonization of Strategically Methylated Quinone Propionic Acid Esters and Amides

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It has been shown that the reduction of quinone propionic acid esters or amides bearing three methyl groups in the so-called "trialkyl lock" positions (*o*-, β-, β-positions) is accompanied by spontaneous lactonization with the release of alcohol or amine, respectively. A new convenient method is reported for introducing the β,β-dimethylpropionic acid side chain onto an appropriate hydroquinone nucleus via alkylative cyclization in methanesulfonic acid. Oxidation of the resulting lactone gives the quinone propionic acid, which can be converted by normal techniques to the corresponding ester or amide derivative. Initial model studies were carried out on pentamethylated systems **6** and **7**. In order to make available quinones of varying redox potential or enhanced solubility in physiological media, methoxy- and amino-substituted quinones **10a**, **10b**, and **17a,b** were synthesized. Upon reduction under mild conditions ($Na_2S_2O_4$), all model esters or amides underwent reductive cyclization with loss of alcohol or amine. In the case of **7a** the intermediate hydroquinone **19** could be isolated and its conversion to **4** with ejection of diethylamine followed by NMR techniques.

Numerous studies have established the importance of the quinone/hydroquinone equilibrium in biological systems. Among examples of the possible practical utilization of such effects in the rational development of new drugs is recent work on bioreductive alkylating agents.[1] A striking example grew out of mechanistic studies on the mode of action of mitomycin C and related synthetic analogues from which emerged an attractive theory that the key step in the biological activity of such materials involves a reductive step which triggers generation of a potent alkylating species.[2] Although definite proof is lacking, the theory is sufficiently attractive to justify further examination. Thus, if a known cytotoxic agent could be bound in a benign or relatively nontoxic form to a quinone such that upon reduction under physiological conditions the material is released in an activated toxic form, a method for the site-specific delivery of an antitumor agent to diseased tissue bathed in a reducing atmosphere might be available. The currently difficult-to-treat solid tumors may represent such a case.[3]

With such long term goals in mind, in this paper we demonstrate the feasibility of the basic delivery concept on model systems. Subsequent papers will deal with specific applications to antitumor and other biological systems as well as purely chemical applications such as the development of new amino protecting groups.

The initial system chosen for evaluation was based on the unique discoveries of Cohen and co-workers[4] who es-

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